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Prevalence of latent tuberculosis infection in Africa: A systematic review protocol

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Prevalence of latent tuberculosis infection in Africa: A systematic review protocol

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Key words: Prevalence, Epidemiology, Latent TB, Africa

ABSTRACT

Introduction: Latent tuberculosis infection (LTBI) remains a major public health problem and one of the major contributors to the pool of active tuberculosis cases. The true burden of LTBI in Africa is not known. Early modelling studies estimate that over a third of the world's population is infected with latent tuberculosis. We propose conducting a systematic review to evaluate the burden of LTBI in Africa reported in studies from 2000 to 2016.

Methods and analysis: We will include studies of any design (except case reports or case series) estimating tuberculin skin test confirmed prevalence of LTBI among the general population in Africa. A comprehensive search of relevant literature will be conducted on electronic databases using common and medical subject heading (MeSH) terms for LTBI, and an African search filter. Risk of bias will be evaluated by assessing all qualifying full-text articles for quality and eligibility using a quality score assessment tool. Standardised data extraction will be carried out after which we will combine odds ratios using random-effects models in Stata 13. Where sufficient data is available, sub-group meta-analyses will be conducted by participant's age group, location and HIV status. This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) 2015 Statement.

Ethics and Dissemination: No ethical issues are foreseen given that this is a protocol for a systematic review of published studies. The results of this study will be published in a peer-reviewed journal and presented at conferences.

Trial Registration number: Systematic review registration: PROSPERO CRD42016037997

Strengths and Limitations of the study

- To our knowledge, this is the first systematic review protocol that will attempt to summarise the burden of TST-confirmed LTBI in Africa
- This study could potentially inform policy and practice to reduce the reservoir of latently infected persons from which new TB cases arise
- This is only the protocol which will be followed by the review in due course; hence, inferences regarding outcomes cannot be reliably made
- The chosen time period is short, however it portrays an important era in Africa as significant gains have been made in the screening and treatment of tuberculosis, which however could have theoretically have had huge impacts on the burden of latent tuberculosis infection on the continent

- **Introduction**

Latent tuberculosis infection [LTBI] is defined as a state in which individuals harbour live *Mycobacterium tuberculosis* without evidence of manifestation of clinical or other symptoms of active disease [1, 2]. Modelling carried over a decade ago estimate that about 33% (> 2 billion people) of the world's population is infected with LTBI [3]. Rates of infection with latent tuberculosis range from 31.2% in Ethiopia [4] and 49% in Uganda [5] to 55.2% in South Africa [6]. High prevalence of LTBI has been reported in at risk populations such as miners (89%) [7], and from 62%-84% in health care workers in high incidence countries [8, 9]. LTBI contributes significantly to the pool of active TB cases within 2–5 years of initial infection [2]. Studies suggest that active tuberculosis will develop in about 5% to 15% of the people with latent infection, and these estimates increase with immunosuppression (30% among those infected with HIV) [10, 11]. Tuberculosis is the second leading cause of mortality from an infectious disease globally after the human immunodeficiency virus (HIV) [5]. In 2013, the World Health Organization (WHO) estimated 9 million new TB cases and 1.5 million tuberculosis deaths globally, of which 80% of the cases and 70% of deaths were reported in low and middle income countries [12].

The pathogenic state of bacterial infection and probability of reactivation depend on the balance between host immunity and the influence of exogenous factors. The following factors substantially increase the likelihood of progression of latent infection: suppression of cellular immunity by HIV infection [10], glucocorticoids [13], organ or hematologic transplantation [14,15], and tumour necrosis factor α inhibitors [16].

Addressing the growing burden of tuberculosis in Africa and the rest of the world requires that individuals are screened and treated for LTBI. Currently it is not possible to directly identify LTBI in humans [1, 10]. LTBI is diagnosed by detecting memory T-cell response against latent infection with *M. tuberculosis* with the use of tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) [17]. Thus, it is imperative to develop tools to improve the diagnostic capacity of current methods. Although currently no standard immunodiagnostic biomarkers have been identified to measure LTBI, there is growing landscape of chemokines, tumour necrosis factor, interleukin growth factors and soluble receptors under development that could improve diagnostic capacity [18].

TST is sensitive, inexpensive and widely used particularly in low resource settings including sub-Saharan Africa [4]. However, TST's specificity for predicting reactivation tuberculosis is poor especially in populations vaccinated with bacilli Calmette-Guẽrin (BCG), as well as being prone to cross-reactivity with environmental non-tuberculosis mycobacterium, and among immunocompromised individuals it has a low sensitivity [17, 19]. Conventional studies on prevalence of LTBI used the TST and were thus hampered by the low specificity of the TST and its cross-reactivity with BCG and exposure to environmental mycobacteria, hence increasing the risk of overestimating LTBI [20]. IGRAs measure in vitro responses of T-cells or peripheral-blood mononuclear cells to *M. tuberculosis* antigens that are not found in BCG and most non-tuberculosis mycobacteria, and thus specificity for *M. tuberculosis* is higher than with the TST [10]. However, recent studies involving serially tested healthcare workers in the United States have shown that false conversions (from a negative to a false positive result) and reversions (from a positive to a false negative result) are more common with IGRAs than with TSTs [19]. In areas with high tuberculosis prevalence, the sensitivity of IGRAs has not shown superiority over the conventional TST [21].

We therefore, propose to conduct a systematic review and meta-analysis to investigate the burden of LTBI among children and adults in Africa.

Objectives

The objective of this review is to conduct a systematic review and meta-analysis of studies assessing the prevalence of TST-confirmed LTBI among the general population in African countries.

Review question

This systematic review will be guided by the following research question: What is the prevalence of TST-confirmed latent tuberculosis infection in the general population in African countries as reported in studies from 2000 to 2016?

Methods

Criteria for considering studies for the review

Inclusion criteria

1. Studies describing the prevalence of LTBI across all age groups, resident in countries belonging to the African continent, in the geographic regions of sub-Saharan and North Africa diagnosed with TST-confirmed *M. tuberculosis* antigens from all ethnicities, socioeconomic and educational backgrounds.

2. Study designs other than case reports and case series will be included. For the purpose of this review, the diagnosis of LTBI should be determined by a TST only.

3. Published articles and unpublished studies will be considered. Articles published in any language, with full English abstracts will be eligible for inclusion.

Exclusion criteria

1. Duplicate publications of the same material. The most complete recent version of a study will be used when the study has been published in more than one journal/conference proceedings.

2. Studies confined to subgroups of people with LTBI (e.g. healthcare workers or miners)

3. Narrative reviews, opinion pieces and letters or any other publications lacking primary data and/or explicit descriptions of the method.

4. Studies deemed to have a low-quality score in the assessment of risk of bias (i.e. ≤ 5 using the Hoy scale) [22].

Search strategy to identify relevant studies

To maximise sensitivity, a broad search strategy will be designed as shown in Table 1. Medical subject heading (MeSH) terms for LTBI will be used in the main search combined with an African search filter developed by Siegfried and colleagues [23, 24] to identify prevalence studies conducted from January 2000 to the African filter comprising country names as well as truncated terms such as 'east* Africa' to ensure that records indexed using regional, rather than country specific terms, will all be included. The African search filter also includes the English name as well as the name of the country in the language relevant to that region. We plan to search for relevant articles in the following databases: PubMed, Web of Science, Africa-Wide: NiPAD, Scopus, and WHOLIS.

In an attempt to identify all relevant articles, the initial search will not be restricted by age or language of publication or publication type. The authors will then independently analyse the text words contained in the title and abstract, and the index terms used to describe the article.

Potentially relevant thesis, bulletins, conference proceedings and reports will also be screened, including ones from the World Health Organization (WHO). Additional publications will be identified from references cited in relevant articles and searches in Google Scholar. Articles will be restricted to publications between 2000 and 2016, and the included studies will not be restricted by language.

Selecting studies for inclusion

Following scrutiny of titles and abstracts, full-text articles will be retrieved for studies meeting with the inclusion criteria. Two authors will independently evaluate and appraise the results of the searches, and studies will then be marked as 1) included, 2) excluded or 3) or marked as pending if the reviewer is uncertain. The independent evaluations will thereafter be compared and discrepancies will be resolved by consensus. If necessary, a third reviewer will act as an arbitrator. A flow chart will be produced to facilitate transparency of the selection process.

Quality appraisal of included studies

A Quality Index based on existing indices will be used to rate the methodological parameters of studies meeting the inclusion criteria [22]. The following items are captured by the 8 item index: sampling, diagnostic heterogeneity, follow-up rates and diagnostic assessment.

A total quality score will be derived from summing the individual item scores and ranges from 0 (lowest) to 16 (highest). The scores will be calculated and documented during the data extraction process.

Study quality will be assessed using a quality assessment tool modified from Hoy et al and as used in Barth and colleagues [25] (Table 2). Based on this tool, studies will be rated as low risk, moderate risk and high risk for scores ≤5, 6–8 and >8, respectively. Discrepancies will be discussed and resolved by consensus between the authors and an independent reviewer. An evaluation of the risk of bias will allow for sensitivity analysis.

Data extraction and management

The process of selecting articles for inclusion will be managed by importing articles into Mendeley software ®. Two independent reviewers will extract relevant data. Fields will include study descriptors (authors, publication year, research design, and length of follow-up), key study measures and outcomes (diagnostic inclusion criteria and rates) and, study entry treatment restrictions, gender and age distribution. Potential caveats of relevant studies, particularly with regard to possible bias introduced with the study, will be noted.

Data synthesis and assessment of heterogeneity

Quantitative data synthesis will include two steps namely, the identification of data sources and documenting numerators and denominators that will be used for prevalence calculations and secondly, the application of the Freeman-Tukey double arcsine transformation to stabilise the variance of study-specific prevalence. This will serve to minimize the influence from studies with extremely small or extremely large prevalence estimates before pooling data using the random-effects meta-analysis [26]. For each study, the reported prevalence will be recalculated to confirm numerators and denominators and, if necessary, adjustments will be made. A random-effects meta-analysis model using the "*metaprop*" routine in STATA® version 13 will be performed to pool prevalence estimates.

The second step will also involve calculating the overall pooled estimate as well as the 95% confidence interval (CI) in order to account for variability between studies. Where possible, a trend analysis will be performed to determine trends of LTBI. Standard errors will be derived from previous studies which presented the corresponding numerator and denominator for prevalence estimates of LTBI.

Heterogeneity from the studies included will be assessed using the I^2 statistic which will be reported as a percentage in order to establish the degree of variation between the studies [27]. The categories of heterogeneity are defined as follows: $\geq$ 76% - 100% considerable, 51% - 75% substantial, 26% - 50% moderate and 25% as low heterogeneity. To further identify heterogeneity, we will use the Chi-squared test (with significance defined at the alpha-level of 10%) and non-overlapping CIs as an indicator of statistically significant differences between studies. Should significant inconsistency between studies be found, sensitivity analysis will be performed to ascertain the sources of heterogeneity. In addition, we will perform subgroup analyses and the findings will be narratively explained together with tables and figures where applicable. Any discrepancies or disagreements will be documented and discussed with a third author.

Assessment of reporting biases

Publication bias will be assessed using symmetry of funnel plots if we identify 10 or more eligible studies.

Reporting of this review

The eligibility criteria of studies and the selection process of relevant articles will be summarised as flow diagrams. This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines [28]. The search strategy and quality appraisal tool will also be published as supplementary documents.

Primary outcome: The primary outcome of this systematic review is to determine the prevalence of TST-confirmed LTBI in Africa.

Secondary outcomes: Secondary outcomes include examining the quality of the studies included in this review, analysing demographic characteristics of cases with TST-confirmed LTBI and trends of LTBI in African countries.

Ethics and Dissemination

No formal ethical review is required as the systematic reviews uses publicly available data. The findings of this systematic review will be disseminated through peer-reviewed journal publications and conference proceedings. To our knowledge, there are no systematic reviews that have specifically looked at the prevalence of TST-confirmed LTBI in Africa. We believe that the findings of this systematic review will have implications for policy, practice and development of diagnostic tools for latent tuberculosis infection, informed by data solely from Africa where the burden of tuberculosis is among the greatest.

Contributors

TJB wrote the first draft and all authors edited the subsequent versions of the draft. TJB and JN developed the protocol, will conduct the searches and extract the data. MEE will oversee the final analysis of the data. All authors have reviewed and accepted the final version of the protocol and given their permission for publication.

Funding

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Competing interests

None declared

Provenance and peer review

Not commissioned; externally peer reviewed.

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Table 1: Search Strategy

SEARCH	MeSH term (modified as needed for use in other databases)
#1	Prevalen*
#2	frequency
#3	rate*
#4	proportion
#5	epidemiolog*
#6	statistic*
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	LTBI
#9	Latent tuberculosis infection*
#10	Latent mycobacterium* tuberculosis
#11	Mycobacterium* tuberculosis
#12	TST
#13	Tuberculin skin test*
#14	Tuberculin test positivity
#15	#8 OR #9 OR #10 OR #11 OR #12 OR #13
#16	*African Search Filter (Appendix 1)*
#17	#7 AND #15 AND #16

Table 2: The quality assessment criteria for prevalence studies

External validity	**Score**
1. Was the study's target population a close representation of the national population in relation to relevant variables?	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of nonresponse bias minimal?	(1 point)
TOTAL:	**(4 points)**

Internal validity	**Score**
1. Were data collected directly from the subjects (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all subjects?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)
TOTAL:	**(6 points)**

Appendix 1: African Search Filter

African Search Filter [22]

(‘‘Africa’’[MeSH] OR Africa*[tw] OR Algeria[tw] OR Angola[tw] OR Benin[tw] OR Botswana[tw] OR ‘‘Burkina Faso’’[tw] OR Burundi[tw] OR Cameroon[tw] OR ‘‘Canary Islands’’[tw] OR ‘‘Cape Verde’’[tw] OR ‘‘Central African Republic’’[tw] OR Chad[tw] OR Comoros[tw] OR Congo[tw] OR ‘‘Democratic Republic of Congo’’[tw] OR Djibouti[tw] OR Egypt[tw] OR ‘‘Equatorial Guinea’’[tw] OR Eritrea[tw] OR Ethiopia[tw] OR Gabon[tw] OR Gambia[tw] OR Ghana[tw] OR Guinea[tw] OR ‘‘Guinea Bissau’’[tw] OR ‘‘Ivory Coast’’[tw] OR ‘‘Cote d’Ivoire’’[tw] OR Jamahiriya[tw] OR Jamahiriya[tw] OR Kenya[tw] OR Lesotho[tw] OR Liberia[tw] OR Libya[tw] OR Libya[tw] OR Madagascar[tw] OR Malawi[tw] OR Mali[tw] OR Mauritania[tw] OR Mauritius[tw] OR Mayotte[tw] OR Morocco[tw] OR Mozambique[tw] OR Mozambique[tw] OR Namibia[tw] OR Niger[tw] OR

Nigeria[tw] OR Principe[tw] OR Reunion[tw] OR Rwanda[tw] OR ‘‘Sao Tome’’[tw] OR Senegal[tw] OR Seychelles[tw] OR ‘‘Sierra Leone’’[tw] OR Somalia[tw] OR ‘‘South Africa’’[tw] OR ‘‘St Helena’’[tw] OR Sudan[tw] OR Swaziland[tw] OR Tanzania[tw] OR Togo[tw] OR Tunisia[tw] OR

Uganda[tw] OR ‘‘Western Sahara’’[tw] OR Zaire[tw] OR Zambia[tw] OR Zimbabwe[tw] OR ‘‘Central Africa’’[tw] OR ‘‘Central African’’[tw] OR ‘‘West Africa’’[tw] OR ‘‘West African’’[tw] OR ‘‘Western Africa’’[tw] OR ‘‘Western African’’[tw] OR ‘‘East Africa’’[tw] OR ‘‘East African’’[tw] OR ‘‘Eastern Africa’’[tw] OR ‘‘Eastern African’’[tw] OR ‘‘North Africa’’[tw] OR

‘‘North African’’[tw] OR ‘‘Northern Africa’’[tw] OR ‘‘Northern African’’[tw] OR ‘‘South African’’[tw] OR ‘‘Southern Africa’’[tw] OR ‘‘Southern African’’[tw] OR ‘‘sub Saharan Africa’’[tw] OR ‘‘sub Saharan African’’[tw] OR ‘‘sub-Saharan Africa’’[tw] OR ‘‘sub-Saharan African’’[tw]) NOT (‘‘guinea pig’’[tw] OR ‘‘guinea pigs’’[tw] OR ‘aspergillums Niger’’[tw])

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	16
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

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Key words: Prevalence, Epidemiology, Latent TB, Africa

ABSTRACT

Introduction: Latent tuberculosis infection (LTBI) remains a major public health problem and one of the major contributors to the pool of active tuberculosis cases. The true burden of LTBI in Africa is not known. Early modelling studies estimate that over a third of the world's population is infected with latent tuberculosis. We propose conducting a systematic review and a meta-analysis to evaluate the burden and risk factors of LTBI in Africa reported in studies from 2000 to 2016.

Methods and analysis: We will include cross-sectional studies, cohort studies and case-control studies estimating either tuberculin skin test (TST) or interferon-gamma release assay (IGRA)confirmed prevalence of LTBI and associated risk factors among people in African countries. A comprehensive search of relevant literature will be conducted on electronic databases using common and medical subject heading (MeSH) terms for LTBI, and an African search filter. Risk of bias will be evaluated by assessing all qualifying full-text articles for quality and eligibility using a quality score assessment tool. Standardised data extraction will be carried out after which prevalence estimates will be pooled using random-effects models in Stata 13. Where sufficient data is available, sub-group meta-analyses will be conducted by risk factors including participant's age group, occupation, location and HIV status. This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta- Analyses Protocols (PRISMA-P) 2015 Statement.

Ethics and Dissemination: No ethical issues are foreseen given that this is a protocol for a systematic review of published studies. The results of this study will be published in a peer-reviewed journal and presented at conferences.

Trial Registration number: Systematic review registration: PROSPERO CRD42016037997

Strengths and Limitations of the study

- To our knowledge, this is the first systematic review protocol that will attempt to evaluate the burden of TST and IGRA-confirmed LTBI in Africa
- This study could potentially inform policy and practice to reduce the reservoir of latently infected persons from which new TB cases arise
- The chosen time period is short, however it portrays an important era in Africa as significant gains have been made in the screening and treatment of tuberculosis, which however could have theoretically have had huge impacts on the burden of latent tuberculosis infection on the continent

Introduction

Tuberculosis is the second leading cause of mortality from an infectious disease globally after the human immunodeficiency virus (HIV) [1]. In 2013, the World Health Organization (WHO) estimated 9 million new TB cases and 1.5 million tuberculosis deaths globally, of which 80% of the cases and 70% of deaths were reported in low and middle income countries [2]. Latent tuberculosis infection [LTBI] is defined as a state in which individuals harbour live *Mycobacterium tuberculosis* without evidence of manifestation of clinical or other symptoms of active disease [3, 4]. Modelling carried over a decade ago reports that an estimated 30% of the world population (1.8 billion people) carried LTBI in 2000 [5]. Rates of infection with latent tuberculosis range from 31.2% in Ethiopia [6] and 49% in Uganda [1] to 55.2% in South Africa [7]. High prevalence of LTBI has been reported in at risk populations such as miners (89%) [8], and from 62%-84% in health care workers in high incidence countries [9, 10]. LTBI contributes significantly to the pool of active TB cases within 2–5 years of initial infection [4]. Studies suggest that active tuberculosis will develop in about 5% to 15% of the people with latent infection, and these estimates increase with immunosuppression (30% among those infected with HIV) [11, 12].

The pathogenic state of bacterial infection and probability of reactivation depend on the balance between host immunity and the influence of exogenous factors. The following factors substantially increase the likelihood of progression of latent infection: suppression of cellular immunity by HIV infection [11], glucocorticoids [12], organ or hematologic transplantation [13, 14], and tumour necrosis factor α inhibitors [15]. Other factors associated with LTBI include age, positive HIV status, working as physicians/nurses or miners, diabetes and malnutrition [1, 7, 8, 9].

Currently it is not possible to directly identify LTBI in humans [3, 11]. LTBI is diagnosed by detecting memory T-cell response against latent infection with *M. tuberculosis* with the use of tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) [16]. Thus, it is imperative to develop tools to improve the diagnostic capacity of current methods. Although currently no standard immunodiagnostic biomarkers have been identified to measure LTBI, there is growing landscape of chemokines, tumour necrosis factor, interleukin growth factors and soluble receptors under development that could improve diagnostic capacity [17].

TST is sensitive, inexpensive and widely used particularly in low resource settings including sub-Saharan Africa [6]. However, TST's specificity for predicting reactivation tuberculosis is poor especially in populations vaccinated with bacilli Calmette-Guẽrin (BCG), as well as being prone to cross-reactivity with environmental non-tuberculosis mycobacterium, and among immunocompromised individuals it has a low sensitivity [16, 18]. Conventional studies on prevalence of LTBI used the TST and were thus hampered by the low specificity of the TST and its cross-reactivity with BCG and exposure to environmental mycobacteria, hence increasing the risk of overestimating LTBI [19]. IGRAs measure in vitro responses of T-cells or peripheral-blood mononuclear cells to *M. tuberculosis* antigens that are not found in BCG and most non-tuberculosis mycobacteria, and thus specificity for *M. tuberculosis* is higher than with the TST [11]. However, recent studies involving serially tested healthcare workers in the United States have shown that false conversions (from a negative to a false positive result) and reversions (from a positive to a false negative result) are more common with IGRAs than with TSTs [18]. In areas with high tuberculosis prevalence, the sensitivity of IGRAs has not shown superiority over the conventional TST [20].

We therefore, propose to conduct a systematic review and meta-analysis to evaluate the burden of TST and IGRA-confirmed LTBI and associated risk factors in Africa.

Objectives

The objective of this review is to conduct a systematic review and meta-analysis of studies assessing the prevalence and risk factors of TST and IGRA-confirmed LTBI among people in African countries.

Review question

This systematic review will be guided by the following research question: What is the prevalence of TST and IGRA-confirmed latent tuberculosis infection in African countries as reported in studies from 2000 to 2016?

Methods

Criteria for considering studies for the review

Inclusion criteria

1. Studies describing the prevalence of LTBI across all age groups, resident in countries belonging to the African continent, in the geographic regions of sub-Saharan and North Africa diagnosed with either TST or IGRA-confirmed *M. tuberculosis* antigens from all ethnicities, socioeconomic and educational backgrounds.

2. Cross sectional, cohort and case control studies will be included. For the purpose of this review, the diagnosis of LTBI should be determined by TST or IGRA.

3. Published articles, thesis, bulletins, reports and conference proceedings will be considered. Articles published in any language, with full English abstracts will be eligible for inclusion.

Exclusion criteria

1. Narrative reviews, opinion pieces and letters or any other publications lacking primary data and/or explicit descriptions of the method.

2. Studies deemed to have a low-quality score in the assessment of risk of bias (i.e. ≤ 5 using the Hoy scale) [21].

Search strategy to identify relevant studies

To maximise sensitivity, a broad search strategy will be designed as shown in Table 1. Medical subject heading (MeSH) terms for LTBI will be used in the main search combined with an African search filter developed by Siegfried and colleagues [22, 23] to identify prevalence studies conducted from January 2000 to the African filter comprising country names as well as truncated terms such as 'east* Africa' to ensure that records indexed using regional, rather than country specific terms, will all be included. The African search filter also includes the English name as well as the name of the country in the language relevant to that region. We plan to search for relevant articles in the following databases: PubMed, Web of Science, Africa-Wide: NiPAD, Scopus, and WHOLIS.

In an attempt to identify all relevant articles, the initial search will not be restricted by age or language of publication or publication type. The authors will then independently analyse the text words contained in the title and abstract, and the index terms used to describe the article. Potentially relevant thesis, bulletins, conference proceedings and reports will also be screened, including ones from the World Health Organization (WHO). Additional publications will be identified from references cited in relevant articles and searches in Google Scholar. Articles will be restricted to publications between 2000 and 2016, and the included studies will not be restricted by language.

Selecting studies for inclusion

Following scrutiny of titles and abstracts, full-text articles will be retrieved for studies meeting with the inclusion criteria. Two authors will independently evaluate and appraise the results of the searches, and studies will then be marked as 1) included, 2) excluded or 3) or marked as pending if the reviewer is uncertain. The independent evaluations will thereafter be compared and discrepancies will be resolved by consensus.

If necessary, a third reviewer will act as an arbitrator. A flow chart will be produced to facilitate transparency of the selection process.

Quality appraisal of included studies

A Quality Index based on existing indices will be used to rate the methodological parameters of studies meeting the inclusion criteria [21]. The following items are captured by the 8 item index: sampling, diagnostic heterogeneity, follow-up rates and diagnostic assessment. A total quality score will be derived from summing the individual item scores and ranges from 0 (lowest) to 16 (highest). The scores will be calculated and documented during the data extraction process. Study quality will be assessed using a quality assessment tool modified from Hoy et al and as used in Barth and colleagues [24] (Table 2). Based on this tool, studies will be rated as low risk, moderate risk and high risk for scores ≤5, 6–8 and >8, respectively. Discrepancies will be discussed and resolved by consensus between the authors and an independent reviewer. An evaluation of the risk of bias will allow for sensitivity analysis.

Data extraction and management

The process of selecting articles for inclusion will be managed by importing articles into EndNote X7 software ®. Two independent reviewers will extract relevant data. Fields will include study descriptors (authors, publication year, research design, and length of follow-up), key study measures and outcomes (diagnostic inclusion criteria and rates) and, study entry treatment restrictions, gender and age distribution. Potential caveats of relevant studies, particularly with regard to possible bias introduced with the study, will be noted.

Data synthesis and assessment of heterogeneity

Quantitative data synthesis will include two steps namely, the identification of data sources and documenting numerators and denominators that will be used for prevalence calculations and secondly, the application of the Freeman-Tukey double arcsine transformation to stabilise the variance of study-specific prevalence. This will serve to minimize the influence from studies with extremely small or extremely large prevalence estimates before pooling data using the random-effects meta-analysis [25]. For each study, the reported prevalence will be recalculated to confirm numerators and denominators and, if necessary, adjustments will be made. A random-effects meta-analysis model using the "*metaprop*" routine in STATA® version 13 will be performed to pool prevalence estimates.

The second step will also involve calculating the overall pooled estimate as well as the 95% confidence interval (CI) in order to account for variability between studies. Where possible, a trend analysis will be performed to determine trends of LTBI. Standard errors will be derived from previous studies which presented the corresponding numerator and denominator for prevalence estimates of LTBI.

Heterogeneity from the studies included will be assessed using the I^2 statistic which will be reported as a percentage in order to establish the degree of variation between the studies [26]. The categories of heterogeneity are defined as follows: ≥ 76% - 100% considerable, 51% - 75% substantial, 26% - 50% moderate and 25% as low heterogeneity. To further identify heterogeneity, we will use the Chi-squared test (with significance defined at the alpha-level of 10%) and non-overlapping CIs as an indicator of statistically significant differences between studies. Should significant inconsistency between studies be found, sensitivity analysis will be performed to ascertain the sources of heterogeneity.

In addition, we will perform subgroup analyses and the findings will be narratively explained together with tables and figures where applicable. Any discrepancies or disagreements will be documented and discussed with a third author.

Assessment of reporting biases

Publication bias will be assessed using symmetry of funnel plots if we identify 10 or more eligible studies.

Reporting of this review

The eligibility criteria of studies and the selection process of relevant articles will be summarised as flow diagrams. This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines [27]. The search strategy and quality appraisal tool will also be published as supplementary documents.

Primary outcome: The primary outcome of this systematic review is to determine the prevalence of TST and IGRA-confirmed LTBI in Africa.

Secondary outcomes: Secondary outcomes include examining the quality of the studies included in this review, assessing trends, demographic characteristics and risk factors of TST and IGRA-confirmed LTBI in African countries.

Ethics and Dissemination

No formal ethical review is required as the systematic reviews uses publicly available data. The findings of this systematic review will be disseminated through peer-reviewed journal publications and conference proceedings. To our knowledge, there are no systematic reviews that have specifically looked at the prevalence of TST and IGRA-confirmed LTBI in Africa. We believe that the findings of this systematic review will have implications for policy, practice and development of diagnostic tools for latent tuberculosis infection, informed by data solely from Africa where the burden of tuberculosis is among the greatest.

Contributors

TJB wrote the first draft and all authors edited the subsequent versions of the draft. TJB and JN developed the protocol, will conduct the searches and extract the data. MEE will oversee the final analysis of the data. All authors have reviewed and accepted the final version of the protocol and given their permission for publication.

Funding

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Competing interests

None declared

Provenance and peer review

Not commissioned; externally peer reviewed.

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Table 1: Search Strategy

SEARCH	MeSH term (modified as needed for use in other databases)
#1	Prevalen*
#2	frequency
#3	rate*
#4	proportion
#5	epidemiolog*
#6	statistic*
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	LTBI
#9	Latent tuberculosis infection*
#10	Latent mycobacterium* tuberculosis
#11	Mycobacterium* tuberculosis
#12	TST
#13	Tuberculin skin test*
#14	Tuberculin test positivity
#15	Interferon-gamma release assay test
#16	Interferon gamma test positive
#17	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	*African Search Filter (Appendix 1)*
#19	#7 AND #17 AND #18

Table 2: The quality assessment criteria for prevalence studies

External validity	**Score**
1. Was the study's target population a close representation of the national population in relation to relevant variables?	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of nonresponse bias minimal?	(1 point)
TOTAL:	**(4 points)**

Internal validity	**Score**
1. Were data collected directly from the subjects (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all subjects?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)
TOTAL:	**(6 points)**

Appendix 1: African Search Filter

African Search Filter [22]

(‘‘Africa’’[MeSH] OR Africa*[tw] OR Algeria[tw] OR Angola[tw] OR Benin[tw] OR Botswana[tw] OR ‘‘Burkina Faso’’[tw] OR Burundi[tw] OR Cameroon[tw] OR ‘‘Canary Islands’’[tw] OR ‘‘Cape Verde’’[tw] OR ‘‘Central African Republic’’[tw] OR Chad[tw] OR Comoros[tw] OR Congo[tw] OR ‘‘Democratic Republic of Congo’’[tw] OR Djibouti[tw] OR Egypt[tw] OR ‘‘Equatorial Guinea’’[tw] OR Eritrea[tw] OR Ethiopia[tw] OR Gabon[tw] OR Gambia[tw] OR Ghana[tw] OR Guinea[tw] OR ‘‘Guinea Bissau’’[tw] OR ‘‘Ivory Coast’’[tw] OR ‘‘Cote d’Ivoire’’[tw] OR Jamahiriya[tw] OR Jamahiriya[tw] OR Kenya[tw] OR Lesotho[tw] OR Liberia[tw] OR Libya[tw] OR Libya[tw] OR Madagascar[tw] OR Malawi[tw] OR Mali[tw] OR Mauritania[tw] OR Mauritius[tw] OR Mayotte[tw] OR Morocco[tw] OR Mozambique[tw] OR Mozambique[tw] OR Namibia[tw] OR Niger[tw] OR

Nigeria[tw] OR Principe[tw] OR Reunion[tw] OR Rwanda[tw] OR ‘‘Sao Tome’’[tw] OR Senegal[tw] OR Seychelles[tw] OR ‘‘Sierra Leone’’[tw] OR Somalia[tw] OR ‘‘South Africa’’[tw] OR ‘‘St Helena’’[tw] OR Sudan[tw] OR Swaziland[tw] OR Tanzania[tw] OR Togo[tw] OR Tunisia[tw] OR

Uganda[tw] OR ‘‘Western Sahara’’[tw] OR Zaire[tw] OR Zambia[tw] OR Zimbabwe[tw] OR ‘‘Central Africa’’[tw] OR ‘‘Central African’’[tw] OR ‘‘West Africa’’[tw] OR ‘‘West African’’[tw] OR ‘‘Western Africa’’[tw] OR ‘‘Western African’’[tw] OR ‘‘East Africa’’[tw] OR ‘‘East African’’[tw] OR ‘‘Eastern Africa’’[tw] OR ‘‘Eastern African’’[tw] OR ‘‘North Africa’’[tw] OR

‘‘North African’’[tw] OR ‘‘Northern Africa’’[tw] OR ‘‘Northern African’’[tw] OR ‘‘South African’’[tw] OR ‘‘Southern Africa’’[tw] OR ‘‘Southern African’’[tw] OR ‘‘sub Saharan Africa’’[tw] OR ‘‘sub Saharan African’’[tw] OR ‘‘sub-Saharan Africa’’[tw] OR ‘‘sub-Saharan African’’[tw]) NOT (‘‘guinea pig’’[tw] OR ‘‘guinea pigs’’[tw] OR ‘aspergillums Niger’’[tw])

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	16
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Prevalence and risk factors of latent tuberculosis infection in Africa: A systematic review and meta-analysis protocol

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Secondary Subject Heading:	Infectious diseases
Keywords:	Prevalence, Epidemiology < TROPICAL MEDICINE, Latent TB, Africa

Prevalence and risk factors of latent tuberculosis infection in Africa: A systematic review and meta-analysis protocol

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ABSTRACT

Introduction: Latent tuberculosis infection (LTBI) remains a major public health problem and one of the major contributors to the pool of active tuberculosis cases. The true burden of LTBI in Africa is not known. Early modelling studies estimate that over 33% of the world's population is infected with latent tuberculosis. We propose conducting a systematic review and a meta-analysis to evaluate the burden and risk factors of LTBI in Africa reported in studies from 2000 to 2016.

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- The chosen time period is short, however it portrays an important era in Africa as significant gains have been made in the screening and treatment of tuberculosis, which however could have theoretically have had huge impacts on the burden of latent tuberculosis infection on the continent

Introduction

Tuberculosis is the second leading cause of mortality from an infectious disease globally after the human immunodeficiency virus (HIV) [1]. In 2013, the World Health Organization (WHO) estimated 9 million new TB cases and 1.5 million tuberculosis deaths globally, of which 80% of the cases and 70% of deaths were reported in low and middle income countries [2]. Latent tuberculosis infection [LTBI] is defined as a state in which individuals harbour live *Mycobacterium tuberculosis* without evidence of manifestation of clinical or other symptoms of active disease [3, 4]. Projections from mathematical models in 2000 estimate that over 30% of the population globally were carriers of LTBI [5]. Rates of infection with latent tuberculosis range from 31.2% in Ethiopia [6] and 49% in Uganda [1] to 55.2% in South Africa [7]. High prevalence of LTBI has been reported in at risk populations such as miners (89%) [8], and from 62%-84% in health care workers in high incidence countries [9, 10]. A significant number of active TB cases arise from people with LTBI within a period of 2-5 years following primary infection [4]. Between 5 to 15% of the people with LTBI progress to active TB and the risk of active TB increases with poor immunity (30% among those infected with HIV) [11, 12].

The pathogenic state of bacterial infection and probability of reactivation depend on the balance between host immunity and the influence of exogenous factors. The following factors substantially increase the likelihood of progression of latent infection: suppression of cellular immunity by HIV infection HIV immunosuppression [11], glucocorticoids [12], blood or organ transplant [13, 14], and tumour necrosis factor α inhibitors [15]. Other factors associated with LTBI include age, positive HIV status, working as physicians/nurses or miners, diabetes and malnutrition [1, 7, 8, 9].

Currently it is not possible to directly identify LTBI in humans [3, 11]. LTBI is diagnosed by detecting memory T-cell response against latent infection with *M. tuberculosis* with the use of tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) [16]. Thus, it is imperative to develop tools to improve the diagnostic capacity of current methods. Although currently no standard immunodiagnostic biomarkers have been identified to measure LTBI, there is growing landscape of chemokines, tumour necrosis factor, interleukin growth factors and soluble receptors under development that could improve diagnostic capacity [17].

TST is sensitive, inexpensive and widely used particularly in low resource settings including sub-Saharan Africa [6]. TST has low sensitivity among people with suppressed immunity and it has low specificity in predicting reactivation TB among people vaccinated with bacilli Calmette-Guẽrin and it is vulnerable to react to environmental non-tuberculosis *mycobacterium* [16, 18]. Conventional studies on prevalence of LTBI used the TST and were thus hampered by the low specificity of the TST and its cross-reactivity with BCG and exposure to environmental mycobacteria, hence increasing the risk of overestimating LTBI [19]. IGRAs has high specificity compared to TST because the former measure cellular response of T-lymphocytes to antigens of M. *tuberculosis* found in BCG and most non-tuberculosis mycobacteria [11]. However, recent studies involving serially tested healthcare workers in the United States have shown that false conversions (from a negative to a false positive result) and reversions (from a positive to a false negative result) are more common with IGRAs than with TSTs [18]. In areas with high tuberculosis prevalence, the sensitivity of IGRAs has not shown superiority over the conventional TST [20].

We therefore, propose to conduct a systematic review and meta-analysis to evaluate the burden of TST and IGRA-confirmed LTBI and associated risk factors in Africa.

Objectives

The objective of this review is to conduct a systematic review and meta-analysis of studies assessing the prevalence and risk factors of TST and IGRA-confirmed LTBI among people in African countries.

Review question

This systematic review will be guided by the following research question: What is the prevalence of TST and IGRA-confirmed latent tuberculosis infection in African countries as reported in studies from 2000 to 2016?

Methods

Criteria for considering studies for the review

Inclusion criteria

1. Studies describing the prevalence of LTBI across all age groups, resident in countries belonging to the African continent, in the geographic regions of sub-Saharan and North Africa diagnosed with either TST or IGRA-confirmed *M. tuberculosis* from all ethnicities, socioeconomic and educational backgrounds.

2. Cross sectional, cohort and case control studies will be included. For the purpose of this review, the diagnosis of LTBI should be determined by TST or IGRA.

3. Published articles, thesis, bulletins, reports and conference proceedings will be considered. Articles published in any language, with full English abstracts will be eligible for inclusion.

Exclusion criteria

1. Narrative reviews, opinion pieces and letters or any other publications lacking primary data and/or explicit descriptions of the method.

2. Studies deemed to have a low-quality score in the assessment of risk of bias (i.e. ≤ 5 using the Hoy scale) [21].

Search strategy to identify relevant studies

To maximise sensitivity, a broad search strategy will be designed as shown in Table 1. Medical subject heading (MeSH) terms for LTBI will be used in the main search combined with an African search filter developed by Siegfried and colleagues [21, 22] to identify prevalence studies conducted from January 2000 to the African filter comprising country names as well as truncated terms such as 'east* Africa' to ensure that records indexed using regional, rather than country specific terms, will all be included. The African search filter also includes the English name as well as the name of the country in the language relevant to that region. We plan to search for relevant articles in the following databases: PubMed, Web of Science, Africa-Wide: NiPAD, Scopus, and WHOLIS.

In an attempt to identify all relevant articles, the initial search will not be restricted by age or language of publication or publication type. The authors will then independently analyse the text words contained in the title and abstract, and the index terms used to describe the article. Potentially relevant thesis, bulletins, conference proceedings and reports will also be screened, including ones from the World Health Organization (WHO). Additional publications will be identified from references cited in relevant articles and searches in Google Scholar. Articles will be restricted to publications between 2000 and 2016, and the included studies will not be restricted by language.

Selecting studies for inclusion

Following scrutiny of titles and abstracts, full-text articles will be retrieved for studies meeting with the inclusion criteria. Two authors will independently evaluate and appraise the results of the searches, and studies will then be marked as 1) included, 2) excluded or 3) or marked as pending if the reviewer is uncertain. The independent evaluations will thereafter be compared and discrepancies will be resolved by consensus.

If necessary, a third reviewer will act as an arbitrator. A flow chart will be produced to facilitate transparency of the selection process.

Quality appraisal of included studies

A Quality Index based on existing indices will be used to rate the methodological parameters of studies meeting the inclusion criteria. The following items are captured by the 8 item index: sampling, diagnostic heterogeneity, follow-up rates and diagnostic assessment. A total quality score will be derived from summing the individual item scores and ranges from 0 (lowest) to 16 (highest). The scores will be calculated and documented during the data extraction process. Study quality will be assessed using a quality assessment tool modified from Hoy et al [23] and as used in Barth and colleagues [24] (Table 2). Based on this tool, studies will be rated as low risk, moderate risk and high risk for scores ≤5, 6–8 and >8, respectively. Discrepancies will be discussed and resolved by consensus between the authors and an independent reviewer. An evaluation of the risk of bias will allow for sensitivity analysis.

Data extraction and management

The process of selecting articles for inclusion will be managed by importing articles into EndNote X7 software ®. Two independent reviewers will extract relevant data. Fields will include study descriptors (authors, publication year, research design, and length of follow-up), key study measures and outcomes (diagnostic inclusion criteria and rates) and, study entry treatment restrictions, gender and age distribution. Potential caveats of relevant studies, particularly with regard to possible bias introduced with the study, will be noted.

Data synthesis and assessment of heterogeneity

Quantitative data synthesis will include two steps namely, the identification of data sources and documenting numerators and denominators that will be used for prevalence calculations and secondly, the application of the Freeman-Tukey double arcsine transformation to stabilise the variance of study-specific prevalence. This will serve to minimize the influence from studies with extremely small or extremely large prevalence estimates before pooling data using the random-effects meta-analysis [25]. For each study, the reported prevalence will be recalculated to confirm numerators and denominators and, if necessary, adjustments will be made. A random-effects meta-analysis model using the "*metaprop*" routine in STATA® version 13 will be performed to pool prevalence estimates.

The second step will also involve calculating the overall pooled estimate as well as the 95% confidence interval (CI) in order to account for variability between studies. Where possible, a trend analysis will be performed to determine trends of LTBI. Standard errors will be derived from previous studies which presented the corresponding numerator and denominator for prevalence estimates of LTBI.

Heterogeneity from the studies included will be assessed using the I^2 statistic which will be reported as a percentage in order to establish the degree of variation between the studies [26]. The categories of heterogeneity are defined as follows: $\geq$ 76% - 100% considerable, 51% - 75% substantial, 26% - 50% moderate and 25% as low heterogeneity. To further identify heterogeneity, we will use the Chi-squared test (with significance defined at the alpha-level of 10%) and non-overlapping CIs as an indicator of statistically significant differences between studies. Should significant inconsistency between studies be found, sensitivity analysis will be performed to ascertain the sources of heterogeneity.

In addition, we will perform subgroup analyses and the findings will be narratively explained together with tables and figures where applicable. Any discrepancies or disagreements will be documented and discussed with a third author.

Assessment of reporting biases

Publication bias will be assessed using symmetry of funnel plots if we identify 10 or more eligible studies.

Reporting of this review

The eligibility criteria of studies and the selection process of relevant articles will be summarised as flow diagrams. This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines [27].

Primary outcome: The primary outcome of this systematic review is to determine the prevalence of TST and IGRA-confirmed LTBI in Africa.

Secondary outcomes: Secondary outcomes include examining the quality of the studies included in this review, assessing trends, demographic characteristics and risk factors of TST and IGRA-confirmed LTBI in African countries.

Ethics and Dissemination

No formal ethical review is required as the systematic reviews uses publicly available data. The findings of this systematic review will be disseminated through peer-reviewed journal publications and conference proceedings. To our knowledge, there are no systematic reviews that have specifically looked at the prevalence of TST and IGRA-confirmed LTBI in Africa.

We believe that the findings of this systematic review will have implications for policy, practice and development of diagnostic tools for latent tuberculosis infection, informed by data solely from Africa where the burden of tuberculosis is among the greatest.

Contributors

TJB wrote the first draft and all authors edited the subsequent versions of the draft. TJB and JN developed the protocol, will conduct the searches and extract the data. MEE will oversee the final analysis of the data. All authors have reviewed and accepted the final version of the protocol and given their permission for publication.

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Competing interests

None declared

Provenance and peer review

Not commissioned; externally peer reviewed.

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Table 1: Search Strategy

SEARCH	MeSH term (modified as needed for use in other databases)
#1	Prevalen*
#2	frequency
#3	rate*
#4	proportion
#5	epidemiolog*
#6	statistic*
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	LTBI
#9	Latent tuberculosis infection*
#10	Latent mycobacterium* tuberculosis
#11	Mycobacterium* tuberculosis
#12	TST
#13	Tuberculin skin test*
#14	Tuberculin test positivity
#15	Interferon-gamma release assay test
#16	Interferon gamma test positive
#17	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	*African Search Filter (Appendix 1)*
#19	#7 AND #17 AND #18

Table 2: The quality assessment criteria for prevalence studies [23]

External validity	**Score**
1. Was the study's target population a close representation of the national population in relation to relevant variables?	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of nonresponse bias minimal?	(1 point)
TOTAL:	**(4 points)**

Internal validity	**Score**
1. Were data collected directly from the subjects (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all subjects?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)
TOTAL:	**(6 points)**

Appendix 1: African Search Filter

African Search Filter [22]

(''Africa''[MeSH] OR Africa*[tw] OR Algeria[tw] OR Angola[tw] OR Benin[tw] OR Botswana[tw] OR ''Burkina Faso''[tw] OR Burundi[tw] OR Cameroon[tw] OR ''Canary Islands''[tw] OR ''Cape Verde''[tw] OR ''Central African Republic''[tw] OR Chad[tw] OR Comoros[tw] OR Congo[tw] OR ''Democratic Republic of Congo''[tw] OR Djibouti[tw] OR Egypt[tw] OR ''Equatorial Guinea''[tw] OR Eritrea[tw] OR Ethiopia[tw] OR Gabon[tw] OR Gambia[tw] OR Ghana[tw] OR Guinea[tw] OR ''Guinea Bissau''[tw] OR ''Ivory Coast''[tw] OR ''Cote d'Ivoire''[tw] OR Jamahiriya[tw] OR Jamahiriya[tw] OR Kenya[tw] OR Lesotho[tw] OR Liberia[tw] OR Libya[tw] OR Libya[tw] OR Madagascar[tw] OR Malawi[tw] OR Mali[tw] OR Mauritania[tw] OR Mauritius[tw] OR Mayotte[tw] OR Morocco[tw] OR Mozambique[tw] OR Mozambique[tw] OR Namibia[tw] OR Niger[tw] OR

Nigeria[tw] OR Principe[tw] OR Reunion[tw] OR Rwanda[tw] OR ''Sao Tome''[tw] OR Senegal[tw] OR Seychelles[tw] OR ''Sierra Leone''[tw] OR Somalia[tw] OR ''South Africa"[tw] OR ''St Helena''[tw] OR Sudan[tw] OR Swaziland[tw] OR Tanzania[tw] OR Togo[tw] OR Tunisia[tw] OR

Uganda[tw] OR ''Western Sahara''[tw] OR Zaire[tw] OR Zambia[tw] OR Zimbabwe[tw] OR ''Central Africa''[tw] OR ''Central African''[tw] OR ''West Africa''[tw] OR ''West African''[tw] OR ''Western Africa''[tw] OR ''Western African''[tw] OR ''East Africa''[tw] OR ''East African''[tw] OR ''Eastern Africa''[tw] OR ''Eastern African''[tw] OR ''North Africa''[tw] OR

''North African''[tw] OR ''Northern Africa''[tw] OR ''Northern African''[tw] OR ''South African''[tw] OR ''Southern Africa''[tw] OR ''Southern African''[tw] OR ''sub Saharan Africa''[tw] OR ''sub Saharan African''[tw] OR ''sub-Saharan Africa''[tw] OR ''sub-Saharan African''[tw]) NOT (''guinea pig''[tw] OR ''guinea pigs''[tw] OR 'aspergillums Niger''[tw])

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Section covered (page)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Protocol is not an update of a previous systematic review
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 (PROSPERO CRD42016037997)
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	None
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	Not funded
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not funded
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting,	7

		time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10-11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication	11

		bias across studies, selective reporting within studies)	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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